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10/530,046	04/01/2005	Yukiko Yokoi	2005_0520A	7940

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WENDEROTH, LIND & PONACK, L.L.P.
1030 15th Street, N.W.,
Suite 400 East
Washington, DC 20005-1503

EXAMINER	
JEAN-LOUIS, SAMIRA JM	
ART UNIT	PAPER NUMBER
1627	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ddalecki@wenderoth.com
eoa@wenderoth.com

Office Action Summary	Application No.	Applicant(s)	
	10/530,046	YOKOI ET AL.	
	Examiner	Art Unit	
	SAMIRA JEAN-LOUIS	1627	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 May 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19,32,34 and 39-41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19, 32, 34, and 39-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *05/25/10*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Arguments

This Office Action is in response to the amendment submitted on 05/25/10. Claims 1-19, 32, 34, and 39-41 are currently pending in the application, with claims 20-31, 33, and 35-38 having being cancelled. Accordingly, claims 1-19, 32, 34, and 39-41 are being examined on the merits herein.

Receipt of the aforementioned amended claims and IDS is acknowledged and has been entered.

Applicant's argument with respect to the rejection of claims 1-19, 32-34, and 39-41 under 35 U.S.C. 103(a) over Onodera in view of Nakamura has been fully considered. Applicant argues that while Nakamura suggests inhibition of crystal growth in fat by sucrose fatty Acid ester (SE), Section 6-3 of the same reference teaches that SE inhibits crystal for transference, i.e. preventing type II crystals of cacao butter from turning into type III crystals with a higher melting point. Thus, when Nakamura is considered as a whole, Nakamura fails to suggest the use of SE for inhibiting crystallization of an amorphous material. Such arguments are not found persuasive as the Examiner maintains that the disclosure of Nakamura et al. would have suggested to one of ordinary skill in the art to try SE for crystal inhibition irrespective of the type of material since Nakamura demonstrated inhibition of larger crystal aggregates in the form of type III crystals. Additionally, the Examiner refers applicant to the Translated

document of Nakamura (pg. 3, paragraph 2 and pg. 24,) that teaches that SE possesses many functions including emulsifying properties, solubilizing properties, foaming properties, inhibition of crystal transition in fats, degradation inhibiting effect of starch as well as lubricative properties and that such emulsifier can be applied to various applications including that of pharmaceutical compositions. Consequently, the Examiner maintains that given that Nakamura teaches that SE was able to inhibit formation of large aggregates of crystals (i.e. type III) from smaller crystals (i.e. type II), one of ordinary skill in the art would have indeed found it obvious to add SE to the pharmaceutical composition of Onodera.

As for applicant's arguments that the clean version of the substitute specification demonstrate that crystallization of amorphous cefditoren pivoxil was inhibited by simply mixing cefditoren pivoxil with a sucrose fatty acid ester has been fully considered but is not found persuasive. The Examiner maintains that such results are not unexpected as the prior art has already established that sucrose fatty acid esters are effective in inhibiting crystal formation. In fact, the Examiner refers applicant to Herrera et al. who teach that already crystallized ß' fats are desired for storage purposes and thus additional crystal formation in the form of ß crystals leads to unacceptable products (See Herrera et al., pg. 321, right col., paragraphs 1-2). Consequently, such phenomenon (i.e. induction of ß crystals) is unwanted (see Herrera, pg. 321, right col., paragraph 3). Herrera et al. thus sought to determine the effects of sucrose ester on nucleation (i.e. formation of crystals) of hydrogenated sunflowerseed oil (see Herrera,

pg. 321, right col., paragraph 4). Importantly, Herrera et al. demonstrated that addition of various concentrations of sucrose ester delayed crystallization and this effect occurred over a periods of at least 2 days and can vary with cooling rate (see Herrera, pg. 323, right col., paragraphs 3-4 and pg. 324, left col., paragraphs 1-3 and tables 3 and 4). As a result, the Examiner contends that the unexpected results purported by applicant are neither unobvious nor unexpected since such results are known in the prior art.

As for applicant's arguments regarding the WO 09/098963 document that discloses experimental data showing that surfactants promotes crystal growth in fat and in aqueous solutions, such arguments are not persuasive as such document is not considered prior art and would not have been available to one skilled in the art at the time of the invention. Moreover, the Examiner disagrees with such arguments as the closest prior art, Bujan et al., teaches otherwise. Specifically, Bujan et al. teach that surfactants depending on the type and concentration showed inhibitory effects on the overall crystallization process of Calcium Hydrogen Phosphate Dihydrate (DCPD) aqueous solutions (see Bujan et al., abstract). Importantly, Bujan et al. demonstrated that all of the surfactants tested inhibited the precipitation of DCPD (i.e. crystal formation of DCPD; see pg. 6465, left col., Section 3.2.2 and pg. 6469, right col., Section 4.2). Consequently, the study of Bujan et al. essentially refutes applicant's argument that surfactant was believed at the time of the invention to accelerate growth in aqueous solution. As a result, the Examiner maintains that Onodera in view of Nakamura does indeed render obvious applicant's instant claims.

For the foregoing reasons, the rejection of record under 35 U.S.C. 103 (a) remains proper and is maintained. However, in view of applicant's amendment, the following modified 103 (a) Final rejection is being made.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-19, 32-34, and 39-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Onodera et al. (U.S. Patent 6,486,149 B2, previously cited) in view of Nakamura (Foods and Food Ingredient Journal of Japan, 1999, Vol. 180, pg. 1, Abstract previously cited and Translated English Document).

Onodera et al. teach a process of making amorphous cefditoren pivoxil with a water soluble high molecular additive (instant claims 33-34; see abstract). Onodera et al. additionally disclose that orthorhombic crystalline Cefditoren pivoxil had several advantages of high purity, high thermal stability and high storage stability, but that it was unsuitable for use in an oral dosage form due to its poor water solubility (see col. 2, lines 44-50). To overcome this poor water solubility, Onodera et al. teach that, "it is known that an amorphous substance generally has a high solubility in water, as

compared with that of the corresponding crystalline substance" (see col. 2, lines 63-66 and col. 3, lines 6-8). In fact, Onodera teaches that his studies have managed to convert the crystalline Cefditoren pivoxil into an amorphous substance having higher water-solubility and that X-ray diffraction demonstrated that the cefditoren pivoxil substance existing in the solid particles is amorphous in nature (instant claims 1, 34, and 39-40; see col. 3, lines 6-9 and lines 36-57 and col. 5, lines 5-14). Onodera et al. further teach that an orally administrable amorphous and water soluble substance of Cefditoren pivoxil is obtained when Cefditoren pivaloyloxymethyl ester is homogenously mixed with a water-soluble high-molecular additive such as a water-solubilized derivative of cellulose and which include hydroxypropylmethyl cellulose (instant claims 3-4, 6-8, and 12-19) and a pharmaceutically acceptable alkali metal salt or alkaline earth metal salt of an alginic acid ester of propylene glycol (see col. 3, lines 46-59; col. 6, lines 48-67 to col. 7, lines 1-43; col. 15 Example 2, wherein hydroxypropylmethyl cellulose is used; and Example 7 spanning col. 20-21). Importantly, Onodera et al. teach that the water-soluble high molecular additive co-existent in admixture with Cefditoren pivoxil in the solid particles can possess a function capable of inhibiting the molecule of Cefditoren pivoxil from undergoing into crystallization (see col. 5, lines 42-46). Additinoally, Onodera et al. teach that the amorphous substance contained in the particles of the aforementioned composition is stable and does not involve crystallization when stored at 40 ºC for 4 months in a sealed container under dry conditions (i.e. cefditoren pivoxil is prevented from being crystallized; instant claim 1; see col. 7, lines 35-42).

Onodera et al. do not teach addition of a sucrose fatty acid ester into the aforementioned composition. Similarly, Onodera et al. do not teach a weight ratio of the sucrose fatty acid ester to the cefditoren pivoxil in a range of 0.008 to 0.816 or that the polymer is in a weight ratio range of 0.008 to 0.816.

Nakamura teaches that sucrose fatty acid ester (SE) has eight hydroxyl groups in the hydrophilic group and so it is possible to manufacture SE ranging from low HLB to high HLB by controlling the degree of esterification (see pg. 1). Nakamura additionally teaches that SE possesses solubilizing properties and can inhibit crystal growth (see pg. 1 of abstract and pg. 22. Section 6-3 of translated document of Nakamura). In fact, Nakamura teaches that SE can be used for other applications including pharmaceuticals (see pg. 25, last paragraph and pg. 26 paragraph 1 of Translated document of Nakamura).

While the exact ratio of the sucrose fatty acid ester and polymer is not disclosed by Onodera, the Examiner contends that it is well within the purview of the skill of the artisan at the time of the invention to adjust the concentration and range of the sucrose fatty acid ester and/or the polymer of the composition during the course of routine experimentation so as to obtain the desirable type of properties (i.e. inhibition of crystals) in the composition. Additionally, because Onodera et al. do not teach addition of polysorbate-80 to the composition, the Examiner contends that the composition is indeed devoid of polysorbate-80 (instant claim 32).

Thus, to one of ordinary skill in the art would have found it obvious to add sucrose fatty acid ester to the composition of Onodera since Nakamura teaches that sucrose fatty acid ester (SE) is able to inhibit the formation of crystals. Moreover, it would have been obvious to one of ordinary skill in the art at the time of the invention to vary the ratio of the sucrose fatty acid ester for the purpose of inhibiting crystals or for solubility purposes. Consequently, one of ordinary skill in the art would have been motivated to add SE and vary its concentration in view of the disclosure of Nakamura with the reasonable expectation of providing a composition that possesses high stability and high dissolvability.

While Onodera does not explicitly teach the retention time of the amorphous characteristics of the aforementioned composition, the Examiner maintains that given that the goal of the invention was to obtain an amorphous cefditoren pivoxil composition, such composition does indeed retain its amorphous character in aqueous medium. Furthermore, given that these characteristics are obtained as a result of mixing the pharmaceutically active ingredient with a sugar fatty acid ester, the Examiner concludes that the modified composition of Onodera would likely maintains its amorphous character by simply adding SE to the composition as taught by Nakamura. If however applicant disagrees, it is incumbent upon applicant to demonstrate through side by side comparative results that the composition of Onodera (not any prior art) does not maintain its amorphous character.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samira Jean-Louis whose telephone number is 571-270-3503. The examiner can normally be reached on 7:30-6 PM EST M-Th.
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/S. J. L. /

Examiner, Art Unit 1627

07/28/2010

/SREENI PADMANABHAN/

Supervisory Patent Examiner, Art Unit 1627